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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,144	08/01/2001	Caili Wang	13403.0004.NPUS00	6422

7590 01/02/2004

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EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/921,144

Applicant(s)

WANG ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-94 is/are pending in the application.
- 4a) Of the above claim(s) 31-86 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30, 87-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-94 are pending.
Claims 20, 22 have been amended.
Claim 94 has been added.
2. Claims 31-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.
3. Claims 1-30, 87-94 are under examination.
4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
5. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 20-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

7. The rejection of claims 1-30, 87-93 under 35 U.S.C. 103(a) as being unpatentable over Glockshuber et al (Biochemistry 29:1362-1367, 1990) and further in view of Pack et al (Biochemistry 31:1579-1584, 1992) and Arndt et al (J. Mol. Biol.

295:627-639, 2000) and Queen et al (U.S. Patent 5,693,762, issued 12/97) and Kammerer et al (Biochemistry 38:13263-69, 1999) is maintained.

The response filed 10/21/03 has been carefully considered but is deemed not to be persuasive. The response states that Glockshuber does not teach or even suggest the use of a heterodimerization sequence and the reference suffers from other limitations such as lower expression levels and the Pack reference does not teach pairwise affinity of any kind to stabilize an antigen binding site and Pack took an entirely different approach to generate the antigen binding site (see page 20-21) and Queen focuses on modifying existing VL and VH dimers (see page 22) and the Arndt reference teaches peptides that form homodimers at physiological buffer conditions (see pages 22-23) and there is nothing in Kammerer suggesting using GABA heterodimerization sequence to stabilize the VL and VH (see page 24). In addition the response states there is lack of motivation to combine the references and states that all of the methods of the VL-VH formats all have profound disadvantages and Glockshuber teaches at most the problem recognized in the art (see page 25-26) and the secondary references do not compensate for this problem because the peptides of Arndt form homodimers under physiological conditions (see page 26) and Kammerer reference requires improper hindsight (see page 27).

In response to these arguments, while it is true Glockshuber's methods to stabilize the FV fragment have some limitations, this is motivation to use the coiled-coils for stabilization to obtain better molecules. Pack clearly teaches heterodimers for stabilizing the scFv molecules which bind antigen and bring binding domains together to

form a bifunctional molecule. Thus, it would have been obvious to bring the VH and the VL domains of an antibody together with a heterodimerization domain as taught by Pack because of the inferiority of the methods to stabilize the molecules of Glockshuber as stated in the response filed 10/21/03. The Queen reference is only used for providing motivation to have human sequences or humanization of the molecules. While some of the peptides do form homodimers in the Arndt reference, the method selects those that form heterodimers in vivo (see abstract). Thus, Arndt specifically recognizes that the peptides need to be heterodimers in vivo which is under physiological buffer conditions as required in the claims. With regard to hindsight reasoning as stated to the Krammerer reference, it would be obvious to use any peptides that form heterodimers because Arndt specifically recognizes the need for such and it would be obvious to use coiled coils that form heterodimers and it is obvious that to form a functional Fv a heterodimer of VH and VL are needed and one would obviously avoid homodimers.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The following is a NEW GROUND of rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 94 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

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was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 94 has been added and adds the limitation that the non single chain has an apparent binding affinity that is at least one order of magnitude higher than a scFv that is stabilized by a linker. The response filed 10/21/03 states that support is in Figure 11B and paragraph 52. Figure 11B is a figure of phage particles and phage binding to antigen. The figure does not support binding of a ccFv that is at least one order of magnitude higher than a scFv. The figure shows phage binding and not the ccFv or the scFv molecules themselves (without the phage). It is known in the art that phage can display multiple numbers of molecules and this can alter the affinity of the molecules or their apparent affinity. Applicant is required to provide specific support for the limitation in the specification as originally filed or remove it from the claim.

Conclusion

10. No claim is allowed.
11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

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Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D.
PRIMARY EXAMINER